Claims 23-34 are pending. Claims 23-33 have been amended to address the clarity issues raised in the Office Action.

The Rejection of Claims 23-33 Under 35 U.S.C. § 112, second paragraph

Claims 23-33 were rejected as unclear. The dependence of all dependent claims was corrected to rely on claim 23. The phrase "an organ which drains into the specimen" was changed to "an organ which drains into a body fluid which drains the organ". It is respectfully submitted that the claims are clear and definite as amended. Applicant thanks the Examiner for pointing out these ambiguities. Withdrawal of this rejection is respectfully requested.

The Rejection of claims 23-34 for Double Patenting

Claims 23-34 are rejected provisionally under the judicially created doctrine of obviousness type double patenting over claims 48-61 of copending Application No. 08/854,727. Applicant provides a terminal disclaimer to overcome this rejection. Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 23-26 and 28 Under 35 U.S.C. § 102(e)

Claims 23-26 and 28 are rejected as anticipated by de la Chapelle (U.S. 5,871,925). This rejection is respectfully traversed.

Two distinct teachings of de la Chapelle are cited in the Office Action as if they were referring to the same subject matter, which they are not. The first teaching of de la Chapelle is that DNA from tumors display a change in short repeat sequences (microsatellites) relative tonormal tissues. The abstract and column 2, lines 51-56 are cited. The second teaching of de la Chapelle is that DNA samples can be obtained from blood or any other body tissue from which DNA can be obtained. Column 3, line 57 and column 5, lines 17-28 are cited. These two teachings refer to two different methods; they cannot be combined as if they refer to the same method.

De la Chapelle teaches two biological phenomena which are related to Hereditary Non-Polyposis Colorectal Cancer (HNPCC). The first is the genetic mutation which causes the disease. The mutation occurs at the *hMSH2* gene locus, which de la Chapelle identifies as a region on human chromosome 2 at region 2p13-21. The second phenomenon is the *result* of the mutation at *hMSH2*. This phenomenon is what de la Chapelle calls replication error (RER), which is also known in the art as microsatellite instability. These two biological phenomenon are clearly and *separately* set out in

paragraphs 1 and 2, respectively, of the "Detailed Description of the Preferred Embodiments" at column 4, lines 35-60.

The first biological phenomenon, the mutation in *hMSH2,* can be found by testing *any* cell of an affected individual, because it is an inherited mutation which is inherited in the germline. See column 5, lines 48-51. The second biological phenomenon, RER, is *only* detected in the *tumors* of HNPCC patients. See column 4, lines 43-59 (emphasis added):

> It is a further discovery of the present invention that **tumors** of individuals who have familial colon cancer display multiple genetic alterations. The alterations are detectable using microsatellite probes or probes to other simple repeated sequences. The multiple genetic alterations phenotype is referred to as "RER+" for replication error. RER+ **tumors** are classified as those in which at least two microsatellite or other simple repeated sequence markers are **somatically** rearranged in the tumor tissue. Patients with RER+ **tumors** have a significantly better prognosis than patients with RER- **tumors,** so this phenotype can be used by the clinician to determine treatments and predict outcomes."

Given this background, it can now be seen that the cited portion of de la Chapelle which teaches using blood or any other body tissue or sample containing DNA refers to the assay which de la Chapelle teaches for the first biological phenomenon, *i.e.,* finding a polymorphism linked to a mutation at chromosome 2p14-16. This portion of the reference (column 5, lines 15-20) *does not* discuss the second biological phenomenon, detecting RER or microsatellite instability. In fact, this portion of the reference *could not* refer to the second biological phenomenon, detecting RER or microsatellite instability, because RER only occurs in **tumors** of HNPCC patients. RER does not occur in the blood or any other cell of HNPCC patients. See column 4, lines 8-34, and Fig. 3, where normal tissue from FCC patients (HNPCC patients) was used as a control against which microsatellite instability in tumors was observed.

Thus de la Chapelle does not anticipate the method of the present claims, which require detection of microsatellite length alterations in a body fluid which drains an organ. Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 27 and 29-34 Under 35 U.S.C. § 103(a)

Claims 27 and 29-34 are rejected as unpatentable over de la Chapelle and further in view of Gonzalez-Qulueta, Merlo, and Ah-See. This rejection is respectfully traversed.

De la Chapelle is discussed at length above with regard to the rejection under 35 U.S.C. §102. As discussed above, de la Chapelle does not teach or suggest detection of microsatellites in any sample *other than tumors*. Thus, claims 29-34, which require detection of microsatellite markers in head or neck, lung, bladder, urine, sputum, and histopathological margins, respectively, are not obvious over de la Chapelle. Similarly, claims 27 and 28 which require detection in a body fluid which drains an organ is not obvious over de la Chapelle.

Gonzalez-Qulueta is cited as teaching instabilities of both tri-and tetra-nucleotide repeats within microsatellite markers. Gonzalez-Qulueta is also cited as teaching detection in bladder and colorectal cancer, and as suggesting detection in any sporadic human cancers. Neither of these teachings of Gonzalez-Qulueta remedies the deficiency in the teaching of the primary reference, *i.e.*, Gonzalez-Qulueta does not teach or suggest detection of microsatellites in any sample *other than tumors*.

Merlo is cited as teaching detection of microsatellite sequences in primary lung tumors. Again, this does not remedy the deficiency in the primary reference, *i.e.*, it does not teach detection of microsatellite changes in any sample other than a tumor sample.

Ah-See is cited as teaching analyzing microsatellite markers in cancers of the head and neck. Once again, this does not remedy the deficiency in the primary reference, *i.e.*, it does not teach detection of microsatellite changes in any sample other than a tumor sample.

Thus, not a single one of the references teaches or suggests the defining characteristic of the claimed methods: detection of cancer in a specimen of a body fluid which drains an organ (claims 23-33) or in a histopathological margin specimen (claim 34). Therefore a *prima facie* case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

Respectfully submitted,

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